Remarks

Claims 1, 15-20, and 22-25 are currently pending in this application. Claims 1, 15-20, and 22-25 remain rejected on arguments laid out in the Office Action mailed on October 28, 2008. No claims have been amended and no new claims have been added.

Applicants respectfully request reexamination and reconsideration of the case. The rejection levied in the Office Action is addressed below.

Introduction

Applicants must admit some frustration with the prosecution of this case. There have only ever been two rejections (and one provisional rejection) levied during the entire prosecution, one of which was addressed trivially in the first Office Action. The second rejection, for lack of enablement, has been maintained through *five* Office Actions, but for ever-changing reasons. Applicants have endeavored to work with the Examiner to address his concerns, including having both in-person and telephonic interviews during which the Examiner indicated that proposed amendments or evidence would indeed be helpful, and also providing extensive declaratory evidence. Unfortunately, it seems impossible for Applicants to succeed in overcoming the rejection because, each time he levies it, the Examiner gives different reasons for his concerns. Each time, Applicants address the articulated concern but Examiner maintains the rejection, now for a new reason. Moreover, the most recent Office Action appears to revert to an earlier articulation of the Examiner's concern, which Applicants understood they had previously addressed and resolved.

Applicants below summarize the entire prosecution history of this case, in order to illustrate the evolving nature of the maintained rejection, as well as the thoroughness of Applicants' responses to each articulation of the rejection. Later, in a final effort to advance prosecution of this case, Applicants present a complete response to *every* version of the lack of enablement rejection levied by the Examiner. As will be clear, Applicants have more than satisfied the legal requirements for enablement, the present claims are patentable to Applicants, and the rejection should be removed.

The presently pending claims relate to a method of delivering a cytotoxic moiety to a neuroectodermal tumor, comprising: administering a composition comprising an agent consisting of chlorotoxin fused to a cytotoxic moiety to an individual having a neuroectodermal tumor, such that the agent binds specifically to the tumor.

The specification includes data from experiments showing the specific binding of synthetic chlorotoxin (TM-601) to tissues from 18 different neuroectodermally derived tumors. Applicants have also provided declaratory evidence demonstrating clinical uptake of chlorotoxin delivered either intracranially or intravenously to subjects suffering from neuroectodermally derived tumors (including gliomas, melanomas, *etc*). The present Applicants discovered, among other things, that chlorotoxin-derived molecules can be used to specifically target neuroectodermal tumors for therapeutic and/or diagnostic purposes, and that conjugates of chlorotoxin linked to cytotoxic moieties can be employed for such purposes. The specification enables these findings, as recited in the present claims.

The initially examined claims referred to a method of treating an individual having a neuroectodermal tumor, comprising administering a pharmaceutical composition comprising an effective dose of chlorotoxin fused to a cytotoxic moiety.

In an Office Action mailed on March 28, 2006 ("the first Office Action") the Examiner issued a rejection under 35 U.S.C. § 112, second paragraph for supposed incompleteness and a rejection under 35 U.S.C. § 112, first paragraph for supposed lack of enablement. The incompleteness rejection was addressed easily and will not be discussed further here.

As regards the enablement rejection, the Examiner alleged that "the specification fails to provide adequate guidance and evidence for how to treat a neuroectodermal tumor. . . by using a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety. . . via various administration routes in vivo" because the claims read on protein therapy *in vivo* and the Examiner argued that protein therapy was supposedly unpredictable at the time of the invention. We note, however, that, in laying out this argument, the Examiner cited articles discussing *gene* therapy.

The Examiner's specific challenge to the claims, as set forth in the first Office Action, was that several neuroectodermal tumors are located in the brain and, according to the Examiner, the blood-brain barrier would present a challenge for gene delivery and protein delivery to such tumors inside the brain. Additional comments by the Examiner in the first Office Action related to difficulties in predicting function from a protein's structure.

Applicant therefore understood that the claims were rejected for lack of enablement because, according to the Examiner, (1) protein therapy in general is unpredictable; and (2) whether chlorotoxin fusions would cross the blood-brain barrier was unpredictable. Applicants filed a response addressing these points on September 14, 2006.

To address the Examiner's comments regarding the alleged unpredictability of protein therapies, Applicants cited several examples of protein therapeutics that have been approved for use for many years well before the filing date of the present application. Applicants further pointed out that problems with gene therapy are not directly translatable to problems with protein therapy.

To address the Examiner's comments regarding the blood-brain barrier, Applicants submitted evidence (including a scientific article) that chlorotoxin fusions can be effectively and specifically delivered across the blood-brain barrier to brain tumor sites. Applicants respectfully pointed out that the Examiner's comments with respect to prediction of protein function from protein structure were misplaced.

In a Final Office Action mailed November 21, 2006 ("the second Office Action"), the Examiner maintained the enablement rejection, but did not explain why Applicants' arguments had not resolved his concern. The Examiner simply stated that Applicants' arguments were "not found persuasive because of the reasons set forth in the preceding Office Action mailed 3-28-06."

The Examiner dismissed the proffered evidence of chlorotoxin fusions crossing the blood-brain barrier by merely stating "it is still unclear whether chlorotoxin-cytotoxic moiety complex can pass through blood brain barrier in a subject", without explaining why it was "still unclear".

The Examiner also repeated his assertion that "the art or [sic] protein therapy was unpredictable at the time of the invention", without commenting on the many approved therapies, and repeated verbatim his comments regarding protein therapy from the first Office Action.

Thus, although Applicants had addressed the concerns stated in the first Office Action, the Examiner was not satisfied. The Examiner offered an apparently new basis for the enablement rejection by asserting that "treatment of different neuroectodermal tumors with different cytotoxic moieties has to be considered individually" and alleged that "one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed."

Applicants now understood that the basis for the lack of enablement rejection levied by the Examiner was that the Examiner required evidence of successful treatment of *each* different kind of neuroectodermal tumor encompassed by the claims, and *each* different kind of cytotoxic moiety. Applicants therefore filed a response along with a Notice of Appeal on May 21, 2007 explaining that the current legal standards for enablement for method of treatment claims, as articulated by *In re Brana*, do not require such evidence. Applicants pointed out and summarized the data provided by the present application, which, as explained below, includes human clinical data and supports methods of treatment of a variety of neuroectodermal tumors using a variety of cytotoxic moieties via a variety of routes of administration. Applicants further provided a Declaration confirming that chlorotoxin fusions do in fact bind specifically to a variety of tumors (including gliomas and melanomas) when delivered by intracavitary or intravenous administration to humans. Applicants explained that the Specification, as confirmed by the Declaration, fully satisfied the proper legal requirements for enablement.

The Examiner mailed an Advisory Action on June 27, 2007 claiming that the present case was not analogous to *In re Brana* (on the ground that *Brana* related to use of a cytotoxic *agent* whereas the present case related to use of a fusion of a cytotoxic agent with a delivery moiety – respectfully, a distinction without a difference!) and again asserting a lack of enablement.

Applicants endeavored to better understand the Examiner's position by requesting an in-person interview. In that interview, on August 27, 2007, the Examiner indicated that the enablement rejection related to his concern for a supposed lack of sufficient evidence of successful *treatment*, but that he did not question the evidence that chlorotoxin fusions could be specifically *delivered* to tumors. The Examiner offered that an amendment reciting "delivery" rather than "treatment" would be helpful.

Applicants therefore filed a response on October 31, 2007. Applicants maintained that the specification is fully enabling for methods of treatment, but amended the claims to methods of delivery in order to advance prosecution of this case.

In an Office Action mailed December 31, 2007 (the third Office Action), the Examiner again maintained the enablement rejection, repeating verbatim the language from the Office Action mailed November 21, 2006 (the second Office Action). In a telephone interview with Applicants' representative on January 16, 2008, the Examiner clarified that he still had concerns that the claims read on methods of treatment rather than on methods of delivery because of the terms "pharmaceutical composition, "effective dose," and "treated." Applicants filed a response on January 24, 2008 amending the claims to remove such terms, in order to advance prosecution of the case.

In an Office Action mailed April 21, 2008 (the fourth Office Action), the Examiner maintained enablement rejection. The Examiner even made reference to a "pharmaceutical composition" even though Applicants had amended the claims to remove the term. The Examiner acknowledged, however, that the specification is "enabling for delivering chlorotoxin fused to a cytotoxic moiety to neuroectodermal tumors in vitro or via intravenous administration or intracavitary injection in the brain in vivo…"

Given the confusing reference in the rejection to language no longer present in the claims, and the fact that the Examiner acknowledged enablement with respect to at least two totally different (one local, one systemic) routes of administration, Applicants requested another telephone interview in order to better understand what more could possibly be required in order to overcome the rejection. In a phone interview with Applicants' representative on July 21,

2008, the Examiner then indicated that he had returned to his concern that the claims encompassed different types of tumors. This time, however, the Examiner specifically mentioned a concern that the claims encompassed delivery to tumors that are *not* located in the brain and that there was a supposed lack of evidence that chlorotoxin can be delivered to different tumors and sites with different administrative routes.

Thus, Applicants had apparently overcome the Examiner's previously-stated concern that chlorotoxin fusions might not cross the blood-brain barrier, but that concern had been replaced with a new concern that chlorotoxin fusions might not bind to tumors that *did not* require crossing the blood brain barrier! Of course the Examiner did not address the previously-provided evidence that intravenously administered chlorotoxin fusions do in fact bind to neuroectodermally derived tumors outside of the brain (*e.g.*, melanomas, as already discussed). Moreover, the Examiner provided no *reason* to justify his stated concern that, in light of the provided evidence that chlorotoxin fusions *do* bind specifically to *various* tumors when administered by *either* local or systemic routes, there might be some reason to doubt that the same would not be achieved with respect to particular other tumors or routes. The Examiner also mentioned a new concern that some cytotoxic moieties might accumulate in the liver.

Applicants filed a response on August 7, 2008 reminding the Examiner, among other things, that (1) the present specification provides evidence of chlorotoxin binding to tumors outside of the brain; (2) Applicants had previously provided evidence that chlorotoxin does not accumulate in the liver; and (3) Applicants had provided evidence that completely different routes of administration are in fact effective, such that there is no reason to doubt the effectiveness of other routes.

In the most recent Office Action mailed October 28, 2008 (the fifth Office Action), the Examiner again maintained the rejection of claims 1, 15-20 and 22-24 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The language used in this Office Action again acknowledges that certain aspects of the claims are enabled, but provides a *more narrow* description of such scope than was presented in the fourth Office Action. Specifically, the fifth Office Action states "the specification, while being enabling for delivering chlorotoxin fused to a radioisotope to neuroectodermal tumors *in vitro* or via

intravenous administration or intracavity [sic] injection of brain *in vivo*, does not reasonably provide enablement for delivering various cytotoxic moieties, including protein or nucleic acid, to a neuroectodermal tumor *in vivo* by administering a composition comprising a chlorotoxin fused to cytotoxic moiety, including, proteins, to an individual via various administration routes…"

Given the repeated morphing of the reasons cited by the Examiner for the enablement rejection, the present response addresses all of the arguments made by the Examiner in the current Office Action or in others. As explained below, Applicants have demonstrated that the present application enables delivery of (1) a range of cytotoxic moieties to a (2) range of tumor types (3) via a variety of routes of administration; that furthermore the chlorotoxin-cytotoxic moiety conjugates have a therapeutic effect *in vivo*; and that the data provided in the specification and in the Declaration by Dr. Alison O'Neill under 37 C.F.R § 1.132 filed May 21, 2007 are sufficiently predictive.

Applicants respectfully submit that, as previously acknowledged by the Examiner, the specification is not required under the law to provide enablement for every species encompassed by the claims. Nonetheless, the Examiner is essentially requiring demonstration of every possible combination of cytotoxic moieties, tumor type, and route of administration encompassed by the claims. Applicants submit that this demand is neither reasonable nor consonant with the law. Furthermore, in laying out grounds for the enablement rejection, the Examiner continues to ignore evidence presented by Applicants refuting the Examiner's allegations of lack of enablement.

Cytotoxic moieties

The presently pending claims recite the use of a conjugate consisting of a chlorotoxin agent fused to a cytotoxic moiety (hereafter "chlorotoxin conjugate"). The Examiner has raised issues as to the range of cytotoxic moieties whose delivery via the claimed method is enabled by the present specification. Stating that the claims read on protein therapy *in vivo*, the Examiner questioned the nature of protein therapeutics.

For example, in the first Office Action, the Examiner alleged that "the specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma, and metastatic melanoma etc. in a tissue sample by using chlorotoxin." In the fifth Office Action, the Examiner acknowledged that the specification is enabling for a method of delivering chlorotoxin fused to a radioisotope to neuroectodermal tumors. Nevertheless, the Examiner continued to repeat his allegation that the specification is not enabling for methods in which the cytotoxic moiety is a protein.

Contrary to the Examiner's remarks, applicants have demonstrated successful delivery of a variety of moieties *including proteins*, to neuroectodermal tumors using chlorotoxin. As mentioned in previously filed response, Applicants have demonstrated that the cytotoxic moieties that can be used in accordance with the invention are not limited to radiolabels such as ^{131}I. At least five chlorotoxin complexes (TM-602, *i.e.*, chlorotoxin covalently linked to biotin; TM-601 radiolabeled with ^{131}I; chlorotoxin labeled with ^{125}I; chlorotoxin-GST fusion protein; and chlorotoxin-GST fusion protein attached to saporin) have been tested and showed neuroectodermal tumor-selective binding and uptake in at least one *in vitro* or *in vivo* system. With regard to delivery of proteins, Applicants have demonstrated that chlorotoxin (which is itself a peptide) when fused to glutathione-S-transferase (GST, a protein) and attached to saporin (another protein) via antibodies (also proteins) is specifically bound and taken up by cancer cells, and effects selective killing of glioma cells. (See, *e.g,*. Example 23 of U.S. Pat. No. 5,905,027, the contents of which the present application incorporates by reference in their entirety.)

Therefore, in contrast to the Examiner's remarks, the specification is enabling for a range of cytotoxic moieties *including proteins.*

Despite Applicants' evidence to the contrary, the Examiner continues to raise issues with protein therapy. Applicants submit that the specification has fully satisfied the enablement requirement as regards to the range of cytotoxic moieties encompassed by the claims.

Tumor types

The Examiner has remarked upon the range of tumor types encompassed by the claims and has alleged that the specification provides enablement for "only" a certain subset of tumor types.

As explained previously, Applicants have presented evidence in the present application that chlorotoxin binds to a variety of tumors, including tumors located both inside and outside the brain. Applicants provided data from experiments on more than 250 frozen or paraffin sections showing the specific binding of synthetic chlorotoxin (TM-601) to tissues from 18 different neuroectodermally derived tumors (*i.e.*, from WHO grade IV: glioblastoma multiformes, WHO grade III: anaplastic astrocytoma, WHO grade II: low grade, WHO grade I: pliocytic astrocytoma, oligodendriomas, other gliomas, gangliomas, meningiomas, ependymomas, metastatic tumors in the brain, medulloblastomas, neuroblastomas, ganglioneuromas, pheochromocytomas, peripheral primitive neuroectodermal tumors, small cell carcinoma of the lung, Ewing's sarcoma, and melanomas (see Examples 8-17 of the Application as filed). The afore-mentioned list presents the entire list of tumors recited in claims 19-20. Tumors among the afore-mentioned list that reside outside the brain include pheochromocytomas (located in the adrenal glands near the kidney; see Figure 4 of the specification as originally filed), small cell lung carcinomas (see Figure 9), and Ewing's sarcoma (a bone cancer; see Figure 12).

Applicants have furthermore demonstrated successful *in vivo* targeting to a variety of tumors, including tumors inside the brain. Intracavitary administration of a chlorotoxin conjugate resulted in specific binding and uptake in high grade gliomas. Intravenous administration of a chlorotoxin conjugate resulted in selective uptake in glioma and metastatic melanoma, two of the claimed neuroectodermally-derived tumors. As elaborated below, such targeting was successful even when the chlorotoxin-cytotoxic moiety conjugate was delivered in such a way that required the conjugate to cross the blood-brain barrier.

Routes of administration

The Examiner has taken issue with the range of routes of administration that are encompassed by the claims, and had mentioned the blood-brain barrier as a deterrent for delivery of chlorotoxin conjugates to brain tumors. The Examiner has also argued, essentially, that protein and peptide therapeutics *may* be eliminated from the body before they may confer a therapeutic effect. In the first and subsequent Office Actions, the Examiner asserted that "It is unclear how the chlorotoxin complex would reach the targeted tumor in the brain via oral administration, intravenous administration, intramuscular administration, subcutaneous administration, or intrathecal administration etc., to a subject."

Applicants have demonstrated in *human clinical trials* that chlorotoxin (a peptide) fused to a cytotoxic moiety (in this case, chlorotoxin labeled with ^{131}I) (1) selectively reaches its target tumor site when administered to a patient either through intracranial or intravenous administration; (2) *passes through the blood-brain barrier* to reach a tumor located in the brain; and (3) has a therapeutic effect *in vivo*. (See Declaration by Dr. Alison O'Neill, submitted May 21, 2007.) That the chlorotoxin-cytotoxic moiety conjugate (which necessarily comprises a peptide, because chlorotoxin is a peptide) has been demonstrated to have a therapeutic effect *in vivo* refutes the Examiner's conjecture that a chlorotoxin conjugate would be eliminated from the body before it elicits a therapeutic effect.

Furthermore, intravenous administration of the chlorotoxin complex was found to result in selective uptake in glioma and metastatic melanoma, two of the claimed neuroectodermally-derived tumors.

The Examiner has continued to argue against enablement for a range of routes of administration by focusing on potential problems with delivery of proteins. Again, the Examiner appears to demand, essentially, that every possible combination of route of administration, cytotoxic moiety, and tumor type encompassed by the claims be explicitly demonstrated in the specification. Applicants reiterate that the specification need not be enabling for every species. Nonetheless, Applicants have demonstrated successful delivery of a chlorotoxin-cytotoxic moiety by two very different routes of administration, including one that

involved successful penetration of the blood-brain barrier. Applicants submit that the positive results with very different routes of administration are more than sufficiently predictive to enable the range of routes of administration encompassed by the claims.

Legal standard for enablement

Applicants have not only met, but also far exceeded, the legal standard for enablement for methods of treatment, let alone for methods of delivering a cytotoxic moiety to a neuroectodermal tumor .[1] As solidified by *In re Brana* (51 F.3d 1560 USPQ2d 1436 (Fed. Cir. 1995), the legal standard for enablement does not require *in vivo* evidence in humans. Accordingly, it is an unusual patent application that is supported by clinical evidence of even one claimed species. The Examiner's demands are excessive and inconsistent with the law.

As Applicants discussed in a response filed May 21, 2007, the Brana court held that

> "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." (51 F.3d 1567)

The court explained its holding by stating:

> "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." (51 F.3d 1567)

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[1]To obviate the Examiner's objections to terminology referring to treatment, Applicants had amended the claims to refer to a method of delivery and had removed phrases such as "pharmaceutical composition" that the Examiner deemed to be related to methods of treatment. Nevertheless, Applicants maintain that claims to methods of treatment are fully enabled by the specification.

Even a cursory search on the USPTO's patent full-text and image database for patents related to peptide and/or protein therapies reveals many issued patents whose claims to methods of treatment are not supported by *in vivo* data in humans. Specifications of many patents do not even include any *in vivo* data whatsoever. To give but a few examples, U.S. Pat. No. 6, 171,818 (the '818' patent) was issued on January 9, 2001 and claims a method for treating cancer comprising administering a protein present in sea snails or hares. Exemplification in the '818 patent was limited to isolation of the protein and *in vitro* experiments involving incubating the protein with cell lines. As another example, U.S. Pat. No. 7,112,329 (the '329 patent) was issued on September 26, 2006 and claims a method for treating pollinosis comprising administering a peptide derived from a Japanese pollen allergen molecule. The specification of the '329 patent describes only *in vitro* experiments, for example, synthesis of peptides, expression of recombinant proteins in bacteria, establishment of T-cell lines and antigen-presenting cell lines for use in experiments, and identification of a peptide epitope involved in pollinosis. For both the '818 and '329 patents, no *in vivo* data was presented, let alone data in humans demonstrating any effect whatsoever. Nevertheless, method of treatment claims encompassing treatment of humans were deemed supported by the specification.

Further examples include patents that do provide *in vivo* data, but do not provide any data in humans. For example, U.S. Pat. No. 7,442,681 (the '681 patent) was issued October 28, 2008 and claims a method of treating a vascular permeability-associated disease comprising administering a peptide inhibitor of p21-activated kinase. The specification of '681 patent provides Examples demonstrating *in vitro* binding, phosphorylation, and membrane permeability studies of p21-activated kinase in the presence of the peptide inhibitor; and *in vivo* permeability studies in mice. U.S. Pat. No. 7,446,183 (the '183 patent) was issued recently, on November 4, 2008, and claims a method of treating a growth hormone deficiency comprising administering a fusion protein that includes an agonist of a growth hormone receptor. The specification of the '182 patent provides Examples demonstrating synthesis of such fusion proteins, expression of such proteins in bacterial cells, *in vitro* bioassays of such fusion proteins, and metabolism of such fusion proteins in rats. Neither the '681 nor the '183 provide data on effects of the peptides

and/or proteins in humans, let alone provide any evidence that the recited proteins have any therapeutic effect *in vivo* in humans.

Applicants further note that the Examiner has based his enablement rejection on his allegation that the state of the art in protein therapy was not sufficiently predictable by the time of the filing of the present application (October 17, 2003). Nevertheless, the '818 patent issued from an application filed September 22, 1998 and the '329 patent issued from an application filed March 9, 1999, dates that precede the filing date of the present application as well as the filing date of the parent of the present application (April 21, 1999).

Applicants have provided evidence far exceeding the legal standard for enablement for method of treatment claims using peptides and/or proteins. Yet the Examiner continues to morph the enablement rejection, relying only arguments citing *potential* issues, each of which is refuted by the *evidence* presented by the Applicant. The Examiner has not articulated whether he disagrees with the legal standard set forth in *In re Brana* and as upheld in the issuing of numerous patents directed to peptide and/or protein therapy.

Applicants respectfully submit that Examination cannot progress until the Examiner has articulated his reasons for holding the present application to a higher standard than that provided by the law.

In light of the above remarks, Applicants hereby requests that the rejection be withdrawn.

Conclusion

Applicants again thank the Examiner for his careful review of the case. Based on the Remarks presented above, Applicants respectfully submit that Claims 1, 15-20, and 22-24 are now in condition for allowance. A Notice to this effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.: 03-1721.

Respectfully submitted,

/Brenda Herschbach Jarrell/

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Brenda Herschbach Jarrell, Ph.D., J.D.
Reg. No.: 39,223

Choate, Hall & Stewart LLP
Patent Group
Two International Place
Boston, MA 02110
Tel: 617-248-5000
Fax: 617-248-5002